PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Risk Factors of Diabetic Retinopathy and Sight-threatening Diabetic Retinopathy: A Cross-sectional Study of 13473 Patients with Type 2 Diabetes Mellitus in Mainland China.
AUTHORS	Liu, Yan; Yang, Jiarui; Tao, Liyuan; Lv, Hui bin; Jiang, Xiaodan; Zhang, Mingzhou; Li, Xuemin.

VERSION 1 - REVIEW

REVIEWER	Ciro Costagliola Dpt of Medicine and Health Sciences University of Molise Campobasso Italy
REVIEW RETURNED	05-Mar-2017

GENERAL COMMENTS	The paper is interesting, concise and well written. In its present form it is suitable for publication

REVIEWER	Gavin Tan singapore national eye centre siingapore
REVIEW RETURNED	17-Mar-2017

GENERAL COMMENTS	This paper has much potential to provide broad epidemiological data on diabetic retinopathy in China. This results are interesting, however the current paper and presentation needs much work. I think the authors will benefit from assistance with medical writing in english. There are multiple areas of syntax and language that need editing. It is not the reviewers role to highlight all of these. Methods: Please highlight if there was sampling methodology or how the cities were selected. Do they represent the chinese population. Your aim is to describe the risk factor for DR in China. If your sampling does not represent the China population you will not meet that objective.

	Please define the diagnostic criteria used. please it is simply history of physician diagnosis of glaucoma please do state as well For post prandial glucose. Was this after a specific glucose load? e.g. 75mg or 100mg glucose challenge? or was this simply taken after Any meal. In which case it would be a significant limitation. For STDR analysis. Please clarify the outcome was STDR vs NODR and NON-STDR. (i.e. the NO DR subjects were included analysis. Please use WHO asian BMI categories. or WHO Internation BMI categories. How were the current BMI categories derived? Why were BC hypertension classification used? is that widely accepted? Results: Again presentation language and syntax does need editing. Discussion We usually use modifiable and non-modifiable risk factors. The reason why longer duration of diabetes increases risk of DR is well established. I don't agree with your hypothesis on age as a risk factor. There is good existing evidence that shows that extremes of older age is associated with lower prevalence of DR because of competing risk of death. Those with poor DM control who would have had severe DR die earlier. "phenomenon was that younger age of DM diagnosis played an important role in DR and STDR progression," I don't agree. But you should have this data. Was younger age of diagnosis in your study independently associated with DR after adjusting for age when the study was performed. If your study does not show this you cannot make this conjecture. you should have age of diagnosis in your data. Discussion has too many conjectures which need to be back with the available evidence in your study or other prior literature. It is also too lengthy and unfocused. please summarise and reduce the unsubstantiated claims. Your study has a huge sample size, so you are powered statistically to find small differences there may not be clinically significant. The FBG is one such example. It would be interesting to look at whether other factors such as socio-economic status, rural-urban divide, affects the DR risk. With such rich data, you should be examining these factors as well. I do expect this to come in future papers.

REVIEWER	Dr Rebecca Thomas Swansea University, UK
REVIEW RETURNED	05-Apr-2017

GENERAL COMMENTS	I read with interest Dr Yan Liu et al's paper entitled risk factors of retinopathy in patients with type 2 diabetes. The novelty of the study was that it was conducted in a Chinese population which confirmed

	all putative risk factors for retinopathy. However, I was concerned about the groups for comparison for STDR. In particular combining those with no DR and Non-STDR into one group. Other studies have previously shown that those without DR and those with non-STDR to be statistically different from each other in modifiable and non modifiable ways. The more usual way would be to compare those without DR to those with STDR or even 3 groups no DR, non-STDR and STDR. Apart from this major concern with the analysis of data there are minor typographical issues throughout the manuscript which would need the written English improving prior to publication. More detail would also be required for the methodology. Authors state blood glucose readings were measured 2hr postprandial was this following an OGTT or was the meal monitored in anyway? were the cholesterol values measured at fasting? Authors state 571 pts were excluded from DR risk analysis and 683 from STDR more detail is needed on why they were excluded and why more excluded from STDR than DR analysis? More detail is required to explain the results in the nomogram otherwise there is no point including it.

REVIEWER	Pedro Romero-Aroca Ophthalmology Service, University Hospital Sant Joan, Institut de Investigacio Sanitaria Pere Virgili [IISPV], Universitat Rovira & Virgili, Reus [Spain]. I have no interest in this study
REVIEW RETURNED	07-Apr-2017

GENERAL COMMENTS	Revision of the manuscript entitled: Risk factors of Diabetic Retinopathy in Patients with Type 2 Diabetes Mellitus in Mainland China A. Summary Cross-sectional study performed in Chine, with a sample of 13473 diabetes mellitus patients. No epidemiological new data was reported. B. Strengths: Despite all data are well known, the study was made in six provinces of Chine and its results can be relevant to known in Chinese population. Study based in a high number of patients (13473) with high number of epidemiological data, very representative of diabetes mellitus population. It is interestingly explanation about importance of gender and age as risk factors. C. Weakness. Weaknesses of this study are: 1. Cross-sectional study that not included new data in knowledge of diabetic retinopathy risk factors. 2. In methods, the diabetic retinopathy and grading should be

	explained more extensively, authors only referred its diagnosis to UK guidelines and an explanation of these should be included in text. 3. English should be revised, it is not correct describe diabetes mellitus treatment as medicine. 4. Effect of age as protective factor should be analyzed more extensively. We are not agreed with genetic explanation for younger diabetic retinopathy prevalence, study include type 1 diabetes mellitus patients, and these patients present a higher incidence of diabetic retinopathy. Minor comments. 1. In introduction authors included 31 references, that represent 73.8% of all references (total = 42 references), also in paragraph 34 of page 4 (introduction) authors included in cross-sectional studies included references 9 to 18, in paragraph 36 in cohort studies references included 19 to 28, and in paragraph 47 in diabetic retinopathy progression included references 9 to 26. Is excessive inclusion of these lot of references in six paragraphs.

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer 1, Dr. Ciro Costagliola:

The paper is interesting, concise and well written. In its present form it is suitable for publication.

Response: Thanks for your kind opinion.

Response to Reviewer 2, Dr. Gavin Tan:

Response:We really appreciate your opinion, it's quite valuable for the improvement of quality of our article, and we have revised our article according to your advice.

This paper has much potential to provide broad epidemiological data on diabetic retinopathy in China.

This results are interesting, however the current paper and presentation needs much work.

I think the authors will benefit from assistance with medical writing in english.

There are multiple areas of syntax and language that need editing. It is not the reviewers role to highlight all of these.

Response: A native speaker reviewed our article and gave us some advice, and we have revised the article accordingly.

Methods:

Please highlight if there was sampling methodology or how the cities were selected.

Do they represent the chinese population.

Your aim is to describe the risk factor for DR in China. If your sampling does not represent the China population you will not meet that objective.

Response: Thanks for your question, due to the limitations of article length, we didn't report the exact sampling procedure. As revised in Strength and Limitations, our study was a cross-sectional study,

while the sampling was not stratified. The sampling procedure was conducted in the following order. Firstly, certain areas in both northern and southern part of China were selected. Then, we contacted local medical institutions and those, which were qualified in DR screening and were willing to participant the program, were included in this study. Finally, standard screening procedures were applied in each screening clinics and patients from local hospitals (1/3), rural communities (1/3) and urban communities (1/3) were enrolled.

Please define the diagnostic criteria used. please it is simply history of physician diagnosis of glaucoma please do state as well

Response: As mentioned above, there were 3 major constituents of enrolled patients. Patients from hospitals were firstly diagnosed with DM by a physician, and then transferred to the screening clinic, and patients from communities were required to bring their medical records when visiting the screening clinic.

For post prandial glucose. Was this after a specific glucose load? e.g. 75mg or 100mg glucose challenge? or was this simply taken after Any meal. In which case it would be a significant limitation.

Response: It's 75mg OGTT. Thanks for your kind opinion, we have revised the method in manuscript.

For STDR analysis. Please clarify the outcome was STDR vs NODR and NON-STDR. (i.e. the NO DR subjects were included analysis.

Please use WHO asian BMI categories. or WHO Internation BMI categories. How were the current BMI categories derived?

Response:

We really appreciated your question. Asian BMI categories were used in our study, when the article was written, there was a mistake as "overweight (≥24 & <27) and obesity (≥27)". In the original data, we defined BMI as underweight (<18.5), normal weight (≥18.5 & <24), overweight (≥24 & <28) and obesity (≥28). We have corrected this mistake in the article, and part of our original data was shown below.

Why were BC hypertension classification used? is that widely accepted?

Response: Yes, we thought BC hypertension is widely used in China and it showed good prognosis in hypertension complications. We just found another study using the same hypertension classification. (Qin X, Li Y, Sun N, et al. Impact of Achieved Blood Pressure on First Stroke in Uncomplicated Grade 1 Hypertension. J Am Heart Assoc. 2017 Mar 8;6(3).)

Results:

Again presentation language and syntax does need editing.

Response: Thanks for your opinion, we have edited this part and we really hope it's suitable for publication standard.

Discussion

We usually use modifiable and non-modifiable risk factors.

Response: We agree, it's more acceptable, and the words has been changed.

The reason why longer duration of diabetes increases risk of DR is well established.

I don't agree with your hypothesis on age as a risk factor.

There is good existing evidence that shows that extremes of older age is associated with lower prevalence of DR because of competing risk of death. Those with poor DM control who would have had severe DR die earlier.

Response: We agree, according to our results, younger age was considered as an independent risk factor for both DR and STDR. However, according to our results, we did find that patients >70 than those in 60-70 had a significant lower incidence of DR (shown in Table 1), while a higher incidence of STDR (shown in Table 2), which might implicate that even though older age is associated with lower incidence of DR, while it's more vision threatened. Thanks for your opinion, we will add this point and relevant references in the article.

"phenomenon was that younger age of DM diagnosis played an important role in DR

and STDR progression," I don't agree. But you should have this data. Was younger age of diagnosis in your study independently associated with DR after adjusting for age when the study was performed. If your study does not show this you cannot make this conjecture. you should have age of diagnosis in your data.

Response: We got this conclusion based on the result that diagnosis age was younger in both DR and STDR, while it's just like you said, we didn't put diagnosis age into logistic analyses, because "age=diagnosis age + diabetes duration" and these three variables showed high collinearity, and eventually younger diagnosis age was dropped. It's not a strong evidence in univariate analyses, thanks for your advice, we have changed this part.

Discussion has too many conjectures which need to be back with the available evidence in your study or other prior literature. It is also too lengthy and unfocused. please summarise and reduce the unsubstantiated claims.

Response: Thanks for your opinion, we have finished the correction of these imprecise sentences, and the content of discussion part was also slightly adjusted.

Your study has a huge sample size, so you are powered statistically to find small differences there may not be clinically significant. The FBG is one such example.

Response: That's true, and we realized that this slightly significant difference had limited meaning in clinical practice.

It would be interesting to look at whether other factors such as socio-economic status, rural-urban divide, affects the DR risk. With such rich data, you should be examining these factors as well. I do expect this to come in future papers.

Response: Thanks for your opinion, we will serious think about it, with the progress of our program, management of disease was also concerned. We will further investigate socio-economic factors that might influence the progression of the disease and we really hope that risk factors in this study and other factors could get much attention.

Response to Reviewer 3, Dr. Rebecca Thomas:

Response: Thanks for your kind opinion, and we have revised our article according to your advice.

However, I was concerned about the groups for comparison for STDR. In particular combining those with no DR and Non-STDR into one group. Other studies have previously shown that those without DR and those with non-STDR to be statistically different from each other in modifiable and non modifiable ways. The more usual way would be to compare those without DR to those with STDR or even 3 groups no DR, non-STDR and STDR.

Response: Thanks for raising this question. We have supplemented the 3-group analysis, and the results were similar to what we have found, as independent risk factors for DR but non-STDR /no DR were exactly the same as DR/no DR, and STDR/ DR but non-STDR analysis showed two new independent risk factors besides those for STDR/non-STDR, which included male sex and Cr. We have added this result into the results section, but not a new table.

Apart from this major concern with the analysis of data there are minor typographical issues throughout the manuscript which would need the written English improving prior to publication.

Response: Thank you for your kind advice. We have asked a native speaker to revise our manuscript and helped to improve our English writing. I hope now

More detail would also be required for the methodology. Authors state blood glucose readings were measured 2hr postprandial was this following an OGTT or was the meal monitored in anyway? were the cholesterol values measured at fasting?

Response: Postprandial glucose readings were measured 2 hours after a 75 mg OGTT in our study, and the cholesterol values were measured after fasting for 8 or more hours. We have added these detailed information in the Methods part.

Authors state 571 pts were excluded from DR risk analysis and 683 from STDR more detail is needed on why they were excluded and why more excluded from STDR than DR analysis? More detail is required to explain the results in the nomogram otherwise there is no point including it.

Response: In DR risk factor analysis, 571 cases were excluded because fundus photographs of both eyes were unrecognized or one eye was diagnosed with R0 and the other eye was unrecognized. 683 cases were excluded in the STDR risk factor analysis because those 2 above reasons, along with one condition when one eye's fundus photograph was graded as unrecognized and the other eye was graded as R1. Therefore, more cases were excluded from STDR analysis than DR analysis.

We have supplemented more explanations about nomogram in our method part.

Response to Reviewer 4, Dr. Pedro Romero-Aroca

We are really glad that you gave us some advice on this study, it's quite valuable for the improvement of quality of our article, and we have revised our article according to your advice.

1. Cross-sectional study that not included new data in knowledge of diabetic retinopathy risk factors.

Response: That's true, owing to the large population in this study and screening clinics in six different provinces, we only chose risk factors that were commonly used in clinical practice.

2. In methods, the diabetic retinopathy and grading should be explained more extensively, authors only referred its diagnosis to UK guidelines and an explanation of these should be included in text.

Response: Thanks for your kind opinion, we have revised this part in method section." Non-STDR was recognized as R0 and R1, and STDR was identified as present if any features of maculopathy (M1), pre-proliferative DR (R2) or PDR (R3) were found."

3. English should be revised, it is not correct describe diabetes mellitus treatment as medicine.

Response: Thanks for your opinion, we have checked the terms in the article.

4. Effect of age as protective factor should be analyzed more extensively. We are not agreed with genetic explanation for younger diabetic retinopathy prevalence, study include type 1 diabetes mellitus patients, and these patients present a higher incidence of diabetic retinopathy.

Response: We agree that it's inappropriate in explanation of age as a protective factor in this study. Another reviewer also suggested that "There is good existing evidence that shows that extremes of older age is associated with lower prevalence of DR because of competing risk of death", we will take this viewpoint and quote relevant references in our article, thanks again for your kind opinion.

Minor comments.

1. In introduction authors included 31 references, that represent 73.8% of all references (total = 42 references), also in paragraph 34 of page 4 (introduction) authors included in cross-sectional studies included references 9 to 18, in paragraph 36 in cohort studies references included 19 to 28, and in paragraph 47 in diabetic retinopathy progression included references 9 to 26. Is excessive inclusion of these lot of references in six paragraphs.

Response: Thanks for your kind opinion, we also quoted some of references which is in introduction part in the discussion part, because we thought it's more comprehensive to quote them first. We will change this strategy in the future, thanks again for your help.

VERSION 2 – REVIEW

REVIEWER	Pedro Romero-Aroca Hospital Universitario Sant Joan Institut de Inveestigacions Sanitaries Pere Virgili (IISPV) University Rovira & Virgili I havo no competing interest in present study or their authors
REVIEW RETURNED	11-May-2017

GENERAL COMMENTS	Revision of the manuscript entitled: Risk Factors of Diabetic Retinopathy and Sight Threatened Diabetic Retinopathy: A Cross-sectional Study in 13473 Patients with Type 2 Diabetes Mellitus in Mainland China A. Summary Cross-sectional study performed in Chine, with a sample of 13473 diabetes mellitus patients. No epidemiological new data was reported.

	B. Strengths: As in previously revision I should appoint that present results can be relevant to known in Chinese population, despite all data are well known in diabetic population. It is interestingly explanation about importance of gender and age as risk factors, factors that in other studies are not significative. C. Commentaries Authors include all my suggestions in new version and should be published.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 4

Reviewer Name: Pedro Romero-Aroca

Institution and Country: Hospital Universitario Sant Joan, Institut de Inveestigacions Sanitaries Pere Virgili (IISPV)

University Rovira & Virgili

Please state any competing interests: I havo no competing interest in present study or their authors

A. Summary

Cross-sectional study performed in Chine, with a sample of 13473 diabetes mellitus patients. No epidemiological new data was reported.

B. Strengths:

As in previously revision I should appoint that present results can be relevant to known in Chinese population, despite all data are well known in diabetic population.

It is interestingly explanation about importance of gender and age as risk factors, factors that in other studies are not significative.

C. Commentaries

Authors include all my suggestions in new version and should be published.

Response to Dr. Pedro Romero-Aroca

Thanks for your kind advice, we hope that our further studies could include more risk factors and provide some basis for clinical practice.